References

1. Coen, E. (1999). The Art of Genes: How Organisms Make Themselves (Oxford: Oxford University Press).
2. Zordan, R., Miller, M., Galgoczy, D., Tuch, B., and Johnson, A. (2007). Interlocking transcriptional feedback loops control white-opaque switching in *Candida albicans*. PLoS Biol. *5*, 1–11.
3. Zacharioudakis, I., Gligoris, T., and Tzamarias, D. (2007). A yeast catabolic enzyme controls transcriptional memory. Curr. Biol. *17*, 2041–2046.
4. Kundu, S., Horn, P., and Peterson, C. (2007). SWI/SNF is required for transcriptional memory at the yeast GAL gene cluster. Genes Dev. *21*, 997–1004.
5. Brickner, D., Cajigas, I., Fondufe-Mittendorf, Y., Ahmed, S., Lee, P., Windom, J., and Brickner, J. (2007). H2A.Z-mediated localization of genes at the nuclear periphery confers epigenetic memory of previous transcriptional state. PLoS Biol. *5*, 81.
6. Peng, G., and Hopper, J. (2002). Gene activation by interaction of an inhibitor with a cytoplasmic signaling protein. Proc. Natl. Acad. Sci. USA *99*, 8548–8553.
7. Bhat, P., and Hopper, J. (1992). Overproduction of the GAL1 or GAL3 protein causes galactose-independent activation of the GAL4 protein: Evidence for a new model of induction for the yeast GAL/MEL regulon. Mol. Cell. Biol. *12*, 2701–2707.
8. Platt, A., Ross, H., Hankin, S., and Reece, R. (2000). The insertion of two amino acids into a transcriptional inducer converts it into a galactokinase. Proc. Natl. Acad. Sci. USA *97*, 3154–3159.
9. Platt, A., and Reece, R. (1998). The yeast galactose genetic switch is mediated by the formation of a Gal4p–Gal80p–Gal3p complex. EMBO J. *17*, 4086–4091.
10. Hittinger, C., and Carroll, S. (2007). Gene duplication and the adaptive evolution of a classic genetic switch. Nature *449*, 677–681.
11. Wang, Y., Krishnan, H., Ghezzi, A., Yin, J., and Atkinson, N. (2007). Drug-induced epigenetic changes produce drug tolerance. PLoS Biol. *5*, 2342–2353.
12. Bird, A. (2007). Perceptions of epigenetics. Nature *447*, 396–398.
13. Ptashne, M. (2007). On the use of the word 'epigenetic'. Curr. Biol. *17*, R233–R236.

Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, Box 595, New York, New York 10021, USA.
E-mail: m-ptashne@ski.mskcc.org

DOI: 10.1016/j.cub.2007.11.017

Evolution: Convergent Eye Losses in Fishy Circumstances

Eye loss has occurred independently several times in Mexican cavefish. A new study shows that some aspects of vision can be restored by crossing cavefish from different populations, suggesting that changes at multiple loci contribute to eye loss.

Jeremy E. Niven

The animals that inhabit caves have fascinated biologists for over 150 years [1]. Cave ecosystems are often isolated from surface ecosystems and strongly energy limited [2] — a combination of factors that produces depauperate ecosystems, which have much in common with island communities. One of the most striking features of caves is surely their darkness — from twilight at the cave mouth to a profound darkness deeper within. The total absence of light makes the eyes of animals living deep within caves redundant and as a consequence many of these animals have lost eye pigmentation, often accompanied by a marked reduction in eye size or even total eye loss [2,3]. Although eye reduction or loss occurs in numerous cave-dwelling animals, including insects and crustaceans [2–4], its evolution and development has been studied most extensively in the Mexican blind cavefish, *Astyanax mexicanus* (Figure 1) [5–9]. These fish are particularly attractive for studying evolution because there are several independent cave populations, which entered caves independently over the past 1,000,000 years. Moreover, descendants of the surface populations from which they arose are still living today and can form fertile hybrids with the cavefish [5–7].

Several recent studies, for instance [5,7], have taken advantage of this ability to produce fertile hybrids between different populations of *A. mexicanus* (= *A. fasciatus*). Hybrids from crosses between cave and surface fish have enabled the identification of twelve quantitative trait loci (QTL) for eye or lens production in populations of *A. mexicanus* [5]. The latest study, published in this issue of *Current Biology* [9], shows that complementation between these loci in different cave populations is sufficient to restore vision in *A. mexicanus*.

Crosses between individuals from surface and cave populations produced progeny capable of responding to a simple behavioural assay of visual function — the optokinetic response — in which the fish's eyes follow dark stripes

Figure 1. Out of sight.

A Mexican blind cavefish (*Astyanax mexicanus*) from the Pachón cave, accompanied by two surface morphs. Image courtesy of Richard Borowsky.

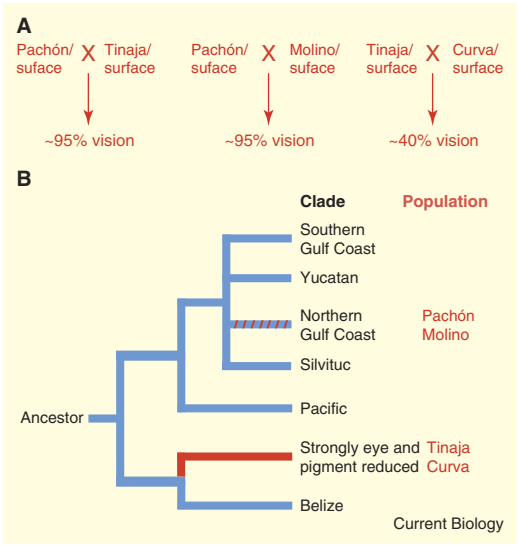

Figure 2. Genetics and phylogeny of Mexican blind cavefish.

(A) Crosses between different cave lineagess produce different percentages of individuals with visual responses. Approximately 95% of the offspring from crossing Pachón/surface with Tinaja/surface or Molino/surface individuals showed visual responses, as opposed to only approximately 40% of the offspring from a cross between Curva/surface with Tinaja/surface individuals. (B) The phylogenetic relationships between populations of *Astyanax*. Seven lineages are shown from Mexico, Guatemala and Belize based on *cytochrome b* mitochondrial DNA haplotypes. Lineages with exclusively surface dwelling species are shown in blue, those with exclusively cave dwelling species in red and those with both in red/blue stripes. Populations from which individuals were derived for crosses are shown in red adjacent to the lineage to which they belong. The phylogeny is adapted from [6].

moving across the visual field [8]. This shows that a single surface allele at each QTL is sufficient to produce a functioning visual system. Crosses in which the surface/cave progeny were crossed with one another produced high proportions (up to 54%) of blind fish (F_2 hybrids). The proportions of blind fish from these crosses suggested that possession of a cave allele at more than 3 or 4 of the eye or lens loci was sufficient to abolish vision. Remarkably, the progeny of crosses between individuals from different blind cavefish populations showed an optokinetic response [8]. This restoration of sight suggests that different cave populations of *Astyanax* carry different cave alleles at non-overlapping sets of eye loci and that in the F_1 hybrids these complement one another to restore vision.

Further crosses were made between individuals from surface populations and from four different cave populations — Curva, Molino, Pachón and Tinaja (Figure 2). Crosses involving lineages derived from the Molino, Pachón and Tinaja populations produced a high proportion of individuals with optokinetic responses whereas crosses between lineages derived from the Curva and Tinaja produced a lower percentage of individuals with visual responses. The high percentages of individuals with vision show that there is complementarity between the loci responsible for eye loss in the Molino, Pachón and Tinaja populations. Similarly, the low percentages of individuals with vision obtained from crosses involving Curva and Tinaja lineages suggest that there is much less complementarity between these populations. This suggests that the Molino, Pachón and Tinaja populations are more genetically distinct than the Curva and Tinaja populations.

These results are consistent with earlier phylogenetic analyses that identified seven distinct *Astyanax* clades [6,9]. The Tinaja and Curva populations are separated by just 12 km and are both part of the 'Strong Eye and Pigment Reduced' clade (Figure 2). This clade, along with another from Belize, is thought to be the remnant of an early invasion of Central America by *Astyanax* from South America following completion of the Isthmus of Panama [6]. Thus, the Tinaja and Curva populations are geographically and genetically close so they are more likely to have cave alleles at the same eye loci. The Pachón and Molino populations are both part of the Northern Gulf Cost clade, which was produced by a second later invasion (Figure 1). However, the Pachón population is geographically distant from both the Molino and Tinaja populations and may also have undergone introgressive hybridization [10]. Thus, individuals from the Pachón population have different alleles at eye loci from both Molino and Tinaja populations.

The precise identity and function of the eye and lens loci identified in *A. mexicanus* is unclear. Cave alleles at these loci may affect the coding regions of genes or *cis*-regulatory elements that affect their expression during development. Recent studies have demonstrated that the lens and retina are independent developmental modules [7]. In addition, as would be expected from populations possessing complementary sets of cave alleles at eye loci, eye development progresses differently in different cave populations [7]. Other studies have implicated the Hedgehog signalling pathway in eye loss because expanded expression of both *sonic hedgehog* and *tiggy-winkle hedgehog* along the midline arrests eye growth and development in cave populations of *Astyanax* [8]. However, neither of these genes maps close to any of the eye or lens loci [5], leaving the identity of these loci unresolved.

Taken together these results suggest that there has been convergent eye loss in at least three independent populations of *Astyanax*. One key question, however, remains unresolved: is this eye loss due to selective pressure to reduce eye size in the dark or to genetic drift in the absence of selective pressure to maintain eye function? Indeed, Darwin suggested that natural selection may not play a role in eye loss: "As it is difficult to imagine that eyes, though useless, could be in any way injurious to animals living in darkness, their loss may be attributed to disuse" [1]. However, recent studies on the vertebrate retina and on insect photoreceptors have emphasised

that there are substantial energetic costs associated with maintaining eyes — even in the dark when they are not signalling — due to the movements of Na^+ and K^+ ions [11,12]. As is the case on islands, the high energetic cost of maintaining neural structures coupled with the limited access to energy would strongly favour a reduction in the size of redundant structures [13,14]. Moreover, the cave alleles at the 12 eye and lens loci identified in the Pachón population of *Astyanax* all cause a reduction in eye size, which is consistent with selection but not drift [5].

Maintenance of brain regions involved in the processing of visual information will also incur substantial energetic costs. It is unclear whether, in the absence of inputs from the eyes, these regions are co-opted for the processing of other sensory modalities in *Astyanax*. There is considerable potential for plasticity during development [15], especially in the nervous system. For example, in eyeless mouse mutants, circuits within the lateral geniculate nucleus that normally receive optic inputs are co-opted to process other extrinsic inputs [16]. This inherent plasticity within the nervous system may facilitate the processing of sensory information from other modalities in cave fish, which have often increased reliance on non-visual senses, particularly mechanosensation. It is also likely that following isolation in caves the visual processing centres in the brain would be reduced in size whilst those processing mechanosensory information would expand.

Some key questions remain about the roles specific eye and lens loci play in eye loss in different *A. mexicanus* populations. It seems crucial to determine their identity and their relationship to genes known to promote eye size reduction such as those in the Hedgehog pathway. Intriguingly, some of these genes may also regulate development of other neural structures such as mechanoreceptors or brain regions.

References

1. Darwin, C. (1859). On the Origin of Species by Means of Natural Selection, or The Preservation of Favoured Races in the Struggle for Life (London: John Murray).
2. Poulson, T.L., and White, W.B. (1969). The cave environment. Science *165*, 971–981.
3. Fong, D.W., Kane, T.C., and Culver, D.C. (1995). Vestigilization and loss of non-functional characters. Annu. Rev. Ecol. Syst. *26*, 249–268.
4. Jones, R., Culver, D.C., and Kane, T.C. (1992). Are parallel morphologies of cave organisms the result of similar selection pressures? Evolution *46*, 353–365.
5. Protas, M., Conrad, M., Gross, J.B., Tabin, C., and Borowsky, R. (2007). Regressive evolution in the Mexican Cave Tetra, Astyanax mexicanus. Curr. Biol. *17*, 452–454.
6. Strecker, U., Faúndez, V.H., and Wilkens, H. (2004). Phylogeography of surface and cave *Astyanax* (Teleostei) from Central and North America from cytochrome b sequence data. Mol. Phyl. Evol. *33*, 469–481.
7. Wilkens, H. (2007). Regressive evolution: ontogeny and genetics of cavefish eye rudimentation. Biol. J. Linn. Soc. *92*, 287–296.
8. Yamamoto, Y., Stock, D.W., and Jeffery, W.R. (2004). Hedgehog signalling controls eye degeneration in blind cavefish. Nature *431*, 844–847.
9. Borowsky, R. (2008). Restoring sight in blind cavefish. Curr. Biol. *18*, R23–R24.
10. Strecker, U., Bernatchez, L., and Wilkens, H. (2003). Genetic divergence between cave and surface populations of *Astyanax* in Mexico (Characidae, Teleostei). Mol. Ecol. *12*, 699–710.
11. Niven, J.E., Anderson, J.C., and Laughlin, S.B. (2007). Fly photoreceptors demonstrate energy-information trade-offs in neural coding. PLoS Biol. *5*, 828–840.
12. Ames, A., Li, Y.Y., Heher, E.C., and Kimble, C.R. (1992). Energy-metabolism of rabbit retina as related to function: high cost of Na^+ transport. J. Neurosci. *12*, 840–853.
13. Niven, J.E. (2005). Brain evolution: getting better all the time? Curr. Biol. *15*, R624–R626.
14. Niven, J.E. (2007). Brains, islands and evolution: breaking all the rules. Trends Ecol. Evol. *22*, 57–59.
15. West-Eberhard, M.J. (1999). Developmental Plasticity and Evolution (Oxford: Oxford University Press).
16. Katz, M.J., Lasek, R.J., and Kaiserman-Abramof, I.R. (1981). Ontophyletics of the nervous system: eyeless mutants illustrate how ontogenetic buffer mechanisms channel evolution. Proc. Natl. Acad. Sci. USA *78*, 397–401.

Department of Zoology, Downing Street, University of Cambridge, Cambridge, CB2 3EJ, UK; Smithsonian Tropical Research Institute, Apartado 0843-03092, Balboa, Ancón, Panamá, República de Panamá.
E-mail: jen22@hermes.cam.ac.uk

DOI: 10.1016/j.cub.2007.11.020

Olfactory Coding: Non-Linear Amplification Separates Smells

How does the nervous system encode complex sensory stimuli? A recent study reveals the fly olfactory system compensates for variability in sensory input as odor representations are restructured for enhanced discriminability and coding efficiency.

Baranidharan Raman and Mark Stopfer

Olfactory stimuli are often spatially and temporally irregular [1]. In addition to the chaotic structures of odor plumes, complex biophysical [2,3] and neural mechanisms [4–6] conspire to make olfactory transduction a sometimes inconsistent and seemingly unreliable process. Yet, remarkably, behavioral and physiological studies show the olfactory system can reliably detect and recognize odorants. In a recent study, Bhandawat *et al.* [7] used the relatively simple olfactory system of the fruitfly *Drosophila* to show how noisy, variable peripheral signals are transformed by early neural circuits into consistent, efficient and distinguishable odor representations.

In *Drosophila*, odorants are detected by a population of ~1200 olfactory receptor neurons (ORNs) in the antenna (~120 in the maxillary palp), each expressing one of ~60 types of odor receptor [8]. Although the ORNs are randomly distributed along the antennae, their axons